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The NICHD Connection

June 2014

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Hot Off the Press: Chronic Stress Linked to Close Quarters

By Shana R. Spindler, PhD

Dr. Amanda Dettmer

High population density may lead to chronic stress, according to a new study by *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) researchers. Their finding offers a possible explanation as to why higher population densities link to negative health outcomes across a variety of animal species.

Signs of chronic stress in animals include slow growth, poor immune function, an inability to reproduce, and in some cases neuron damage. The body responds to stress with a release of hormones, called glucocorticoids, into the bloodstream. When stress is short-lived, a feedback loop signals the brain to stop producing these hormones. But when stress is chronic, some of the hormones, in particular cortisol, remain in the bloodstream prolonging the stress response. Several research groups have shown that diverse animal species have higher glucocorticoid levels when living in dense populations.

"Population density can have potentially deleterious effects on developmental outcome and particular health issues for humans and animals alike, " said Dr. Amanda Dettmer, postdoctoral fellow in Dr. Stephen Suomi's lab and lead author of the study. One reason it's been difficult to test the link between population density and chronic stress is because researchers have traditionally collected cortisol from blood or saliva, a measure of acute stress. In 2006, Dr. Jerrold S. Meyer's lab at the University of Massachusetts Amherst developed a method to extract cortisol from hair samples. "Rather than being a snapshot of what the individual is going through right now, it's more of a panorama of what the individual has been through over the last several months," Dr. Dettmer said.

In collaboration with their colleagues at the University of Massachusetts, Dr. Dettmer measured hair cortisol levels in two populations of animals: one high

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Letter from the Editor

Drum roll please… June marks *The NICHD Connection*'s four-year anniversary! Since our first issue, we've had over 100 volunteer writers, more than 40 event recaps, plenty of helpful "Former Fellow Follow-ups," and of course non-stop coverage of NICHD award-winning research. If you're new to the NICHD, I encourage you to check out the **newsletter archives** or access theme-specific articles by clicking the "Regular Features" links on the left side of the **newsletter home page**.

This month's issue is all about NICHD research. First, learn about **exciting new research from the Suomi lab** in our "Hot Off the Press" column. Then, enjoy as our volunteer contributors **recap the Tenth Annual NICHD Fellows Meeting**—the next best thing to being there.

I've said it before, and I'll say it again: it's an honor to produce this newsletter with all of you. Your research never ceases to amaze me, and I genuinely hope this publication helps each of you reach your career goals as you make significant contributions to the health of our community.

Your Editor in Chief,
Shana R. Spindler, PhD

Questions, comments, ideas? Please send emails to **Shana.Spindler@gmail.com**

Hot Off the Press: Chronic Stress Linked to Close Quarters

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and one low density. The high-density group resided in an indoor-outdoor enclosure containing multiple perches, swings, and enrichment devices. In contrast, the low-density group lived in a five-acre outdoor enclosure. The high-density living conditions linked to higher levels of hair cortisol across all ages. The results suggest that individuals in high-density populations experience chronic stress to a greater extent than those in less crowded conditions.

This is the first study to show that increased population density links to higher levels of hair cortisol, indicating chronic stress. The team published their work in *Psychoneuroendocrinology*. While the study shows a correlation, not causation, Dr. Dettmer hopes to identify what factor in high-density living conditions contributes to increased stress in individuals.

» Dettmer AM, et. al. (2014). *Psychoneuroendocrinology* 42, 59-67.

The Tenth Annual NICHD Fellows Meeting Recap

Fellows gathered at the National Museum of the American Indian in downtown Washington D.C. for a day away from the lab—but not away from science! The annual fellows retreat is always a highly anticipated event where fellows can share research stories and learn firsthand about exciting career opportunities. This year's retreat was no exception. Keynotes by a Nobel Prize winner and a successful—very successful—business owner, intriguing talks by NICHD fellows, and scientific updates from some of the institute's principal investigators packed the day. A full agenda can be found at http://retreat.nichd.nih.gov.

Missed this year's meeting? Fear not. Several NICHD fellows have graciously volunteered to recap each of the talks here.

Physicists and Biologists, Unite!

By Valerie Virta, PhD

"I wonder what I learned in graduate school? Maybe they didn't know anything back then," joked Dr. Eric Wieschaus, professor at Princeton University and 1995 Nobel Prize winner, referring to how much developmental biologists have discovered over the past few decades. Dr. Wieschaus delivered the morning's keynote address, which focused on the relationship between gene activity and cellular mechanics.

Dr. Eric Wieschaus

Once cells know what they are by gene expression, that almost immediately translates to cell behavior, Dr. Wieschaus explained. To examine this phenomenon, his lab uses microscopy and mathematical modeling to study cellular invagination during *Drosophila* gastrulation, a time during fruit fly development that lacks cell division, has very little migration, and, most importantly, is fast!

Dr. Wieschaus relies on two recent advances in microscopy: two-photon microscopy and light-sheet confocal microscopy. These, combined with a software program called the Embryo Development Geometry Explorer (EDGE I & EDGE II), enable a dynamic reconstruction of cellular morphogenesis. But what really gives his work an "edge" is that his team mathematically models the physical forces exerted by cells during invagination to develop hypotheses about cell shape changes. "My lab has been invaded by

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The Tenth Annual NICHD Fellows Meeting Recap

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physicists," he said, with a smile.

Their goal using mathematical models for cell mechanics is to find the simplest possible model that accounts for all quantitative data. Oleg Polyakov, a recently defended graduate student, constructed a mathematical model that treated invagination like a bunch of springs, or an elastic surface. During invagination, cells first pinch into a placodal shape and then eventually undergo dramatic cell shape changes. The team hypothesized that, like a spring, the cell stores energy in the lateral membrane during the first stage of shape change and releases it to apical-basal stretchiness during the next. The key is the relative stretchiness between the lateral and basal surfaces.

To test this model, Dr. Wieschaus's group injected inert fluorescent beads into the cytoplasm of the gastrulating fly embryo to see if cellular flow followed the predictions of the model. They found that cells flowed as if they were a continuous viscous liquid. This led them to ask if a lateral membrane is necessary for invagination. Using a double mutant that fails to incorporate membranes during celularization, lightheartedly called *slam dnk* (pronounced slam-dunk), they still observed viscous movement, but ultimately invagination failed and the embryo died.

Their results led them to conclude that the lateral plasma membrane is needed to store potential energy like a spring, driving the second phase of invagination. Dr. Wieschaus urged the audience to think about invagination during fruit fly gastrulation as global movements rather than the behavior of individual cells. To conclude his talk, he offered that the right way to think about the mechanics of cell shape change is to unite the views of physicists and biologists, an approach that clearly has worked for him.

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The Tenth Annual NICHD Fellows Meeting Recap

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Of Mice, Zebrafish, and Men: Fellow Presentations 1 & 2

By Joanna Cross

Dr. Amber Stratman

After an engaging welcome and keynote address, the morning continued with two fellow presentations by Dr. Amber Stratman and Dr. Katerina Nella.

Dr. Amber Stratman, a postdoc in Dr. Brant Weinstein's lab, started the session with a new way of thinking about cancer therapy. Tumors rely on a good blood supply, making anti-angiogenic therapies—which help prevent the formation of blood vessels—a promising therapeutic approach. However, some tumors evade these therapies by increasing levels of signaling molecules in angiogenic (blood vessel forming) pathways. One of these molecules, Vascular Endothelial Growth Factor (VEGF), relies on the recycling of another molecule called phosphoinositide.

Using both zebrafish and cell culture, Dr. Stratman inhibited the recycling of phosphoinositide to prevent angiogenesis. Excitingly, the method was successful. Tumors increased their levels of VEGF to compensate, which in turn depleted phosphoinositide more rapidly. Dr. Stratman continued her studies in a tumor-producing mouse model and discovered that inhibiting phosphoinositide recycling indeed reduced tumor growth! Dr. Stratman is currently carrying out chemical screens to identify and validate compounds that inhibit phosphoinositide recycling to continue this novel approach to cancer therapy.

If this wasn't engaging enough, Dr. Katerina Nella moved the session into

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The Tenth Annual NICHD Fellows Meeting Recap

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a more clinical setting by presenting her work, in collaboration with Dr. Deborah Merke, on a new method for administering therapies to patients suffering from Congenital Adrenal Hyperplasia (CAH). These patients have depleted cortisol levels, which are responsible for circadian rhythms (including sleep cycles). Conventional therapy is administered orally and focuses on replacing the steroid hormones cortisol and aldosterone in combination with preventing excess of a third steroid hormone, androgen. However, this method is often ineffective in suppressing androgen levels without administering greater than physiological normal cortisol levels.

Dr. Nella is conducting a Phase I-II clinical trial to test a new administration method—Continuous Subcutaneous Hydrocortisone Infusion (CSHI). This method uses a pump under the skin that keeps cortisol at typical physiological levels using similar or lower doses than conventional treatment. The trial assessed four adult patients on this new treatment method over the course of six months. The patients were using conventional oral administration at the start of the trial, which functioned as the baseline. At two and six months, Dr. Nella conducted serial hormone sampling to investigate levels of 17OH-Progesterone, an important biomarker of CAH androgen control. To conclude a memorable session, Dr. Nella informed us that the trial has been successful so far, with all patients tolerating CSHI well, showing significant reduction of androgens.

Dr. Katerina Nella

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The Tenth Annual NICHD Fellows Meeting Recap

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Moving Forward: Scientific Update with Dr. Jennifer Lippincott-Schwartz

By Libby Barksdale, PhD

Dr. Jennifer Lippincott-Schwartz

Muscle fibers and cardiomyoctes, or heart cells, are obvious examples of cells that contract. But contraction is a fundamental property of ***all*** cells and is necessary for cell motility, which, in turn, is necessary for numerous developmental and regenerative processes. Most motile cells in multicellular organisms utilize a crawling movement, and this was the focus of Dr. Jennifer Lippincott-Schwartz's Scientific Update.

Cells "crawl" by constantly extending and retracting their lamellae, the flattened portions of cells pointed in the direction of movement. Lamellae are enriched in actin filaments and myosin II—the same proteins responsible for muscle contraction—as well as focal adhesions that connect cells to their substrates. Using a combination of cutting-edge imaging and protein labeling techniques, Dr. Lippincott-Schwartz and her lab visualized the 3D organization of actin and myosin in lamella to better understand contractile activity in moving cells.

There are three types of actin filament-based fibers in the lamella: arcs, dorsal stress fibers, and anchor stress fibers. "Think about a tent," Dr. Lippincott-Schwartz said. "Arcs create tension on dorsal stress fibers analogous to how canvas puts stress on a tent to shape it." The anchor stress fibers serve as "stakes for the tent." This is certainly a helpful image, but tents are stationary…and not flat, unless something has gone terribly wrong. So how does this translate into a moving cell and a flattened lamella?

At the "front" of the lamella is a region called the lamellipodium, where a meshwork of actin filaments continuously builds up and breaks down, driving the extension and retraction, respectively, of the leading edge. Occasionally during a retraction phase, the cell lays down a focal adhesion, which anchors the cell in the new position. After multiple cycles, the cell moves incrementally forward. At the same

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The Tenth Annual NICHD Fellows Meeting Recap
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time, myosin II clusters individual actin filaments together and rearranges them into arcs. Dorsal stress fibers join the focal adhesions with the newly formed arcs (think tent stakes). As new arcs form, more mature arcs move away from the leading edge and farther back into the lamella. Myosin II builds up on the mature arcs and, similar to sarcomeric contraction in muscles, pulls on the arcs causing them to contract. Thus as the actin arcs contract and move away from the cell edge, the dorsal stress fibers joined to them behave as levers pivoting at focal adhesion "hinges" to pull down the dorsal surface of the lamella.

To test this model, the lab inhibited the dorsal contractile system, which resulted in a puffy lamella. But even more telling, adding the contractile system induced flattening behavior in a non-flat cell. So if you're having trouble setting up your tent on a camping trip this summer, just think about a cell's dorsal contractile system. You'll get it.

Raising a Toast to Obesity Resistance: Fellow Presentations 3 & 4
By Apratim Mitra, PhD

The post-lunch fellow presentations showcased two important health issues facing society at present—obesity and alcoholism. First, Dr. Edra London (Stratakis lab) covered the contribution of RIIα, an enzymatic subunit of protein kinase A (PKA), to diet-induced obesity (DIO) in mice. Second, Dr. Nader Shahni Karamzadeh (Gandjbakhche lab) presented his use of a sophisticated computational approach to find characteristics that distinguish brains of alcoholics from normal subjects.

PKA is an important component of metabolic pathways linked to obesity, but the contribution of its widely expressed subunit RIIα is unclear. Dr. London and colleagues found that disruption of RIIα produced leaner mice that were resistant to DIO, supporting their hypothesis that RIIα plays an important role in the process. Interestingly, this effect appeared limited to female mice, which not only showed improved glucose tolerance, but also reduced intake of the high-fat diet (HFD).

Dr. Edra London

Dr. London surmised that lowered body fat and the altered preference for fatty feed were possibly linked to changes in PKA signaling. They confirmed this with subsequent experiments that revealed striking increases in PKA activity in brain and adipose tissue of the RIIα knockout (KO) mice. In summary, removal of RIIα resulted

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The Tenth Annual NICHD Fellows Meeting Recap

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in leaner mice as a result of lower fat intake and higher energy expenditure that correlated with higher PKA activity. Dr. London emphasized the potential of RIIα as a therapeutic target for obesity and the importance of the RIIα-knockout mice for understanding the role of PKA in food intake and energy balance.

Next we learned about a novel mechanism to identify alcoholism. The detrimental effects of excessive alcohol consumption on various functions of the brain are well known. Researchers use electroencephalography (EEG) to measure and record brain activity over short periods of time with electrodes attached to the scalp. Dr. Karamzadeh asked whether it was possible to distinguish between alcoholics and normal subjects on the basis of brain activity measured via EEG. To this end, he developed a novel technique, termed Relative Brain Signature (RBS). In brief, he extracted meaningful features from EEG profiles of known alcoholic and control subjects to generate a "fingerprint" of the respective groups. Dr. Karamzadeh then used these fingerprints to calculate the likelihood that a patient was alcoholic or not. Validation of RBS using a public repository of EEG data revealed its impressive accuracy, as this method was able to correctly classify individuals 85 percent of the time. Dr. Karamzadeh expressed the hope that his results could lead to identification of functional biomarkers and possible early warning signs of alcoholism.

Dr. Nader Shahni Karamzadeh

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Genetic Basis of Brittle Bones: Scientific Update with Dr. Joan Marini

By Sudhir Rai, PhD

The scientific update sessions were designed to highlight some of the latest research updates in biomedical research. For the second update of the day, Dr. Joan Marini, chief of the NICHD Bone and Extracellular Matrix branch, presented some of her recent findings on the genetic basis of bone disease.

Osteogenesis Imperfecta (OI), also known as brittle bone disease, is a clinically heterogeneous connective tissue disorder characterized by bone fragility and deformity. OI is usually caused by mutations in type I collagen, a major protein component of extracellular matrix in bone and skin. These mutations are usually dominant and account for 85 to 90 percent of OI cases. An important question, however, is what causes recessive OI. One day, while Dr. Marini and her colleagues sat around a conference table, they began listing proteins that interact with type I collagen. Then, they went down the list.

With the power of molecular biology and whole exome sequencing, she identified and characterized numerous genes involved in OI, such as collagen prolyl 3-hydroxylation complex, cartilage associated protein (CRTAP), LEPRE1, and PPIB. She also identified additional disease loci responsible for recessive OI, such as FKBP10, SERPINH1, SP7/OX, and SERPINF1. While FKBP10 and SERPINH1 code for collagen chaperones resident in the ER, products of the latter two genes are not directly involved in collagen production or secretion, but instead are key factors in osteoblast differentiation and activity.

Dr. Joan Marini

Thanks to Dr. Marini's research, we have a better understanding of how very rare mutations in specific genes affect the structure of type I collagen, and how this leads to the OI symptoms observed in these patients. This research opens doors for basic and clinical scientists to further explore the mechanism behind OI disease and hopefully develop versatile treatment tools.

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Do What You Love: Career Keynote with Dr. Sherri Bale

By Michael Dambach, PhD

In today's challenging job market, many fellows are choosing career paths outside of the traditional academic setting. Breakthroughs in basic research coupled with technological innovation are creating new opportunities that did not exist in the past for scientists. However, the path to obtaining a position outside of the university setting is not always intuitive, leading to frustration and uncertainty. That's what made this year's career keynote address at the tenth annual NICHD fellows retreat all the more refreshing.

Former NIAMS section head Dr. Sherri Bale presented "Life after NIH: taking the road less traveled," and indeed it was. Dr. Bale believes she was "born a scientist." It just took her a while to come to this realization. She attended four different colleges along the way and worked as an EMT, cytogenetics technician, waitress, and bartender before earning her Bachelor's degree in biology from Clark University. On being a bar tender, Dr. Bale quipped, "it was fun and sort of like chemistry." However, it was her experience as a cytogenetics tech in the chromosome biology lab at Massachusetts General Hospital that ultimately led her to the University of Pittsburgh, where she earned a MS in genetic counseling, followed by a PhD in statistical genetics.

Dr. Sherri Bale

She next followed her then husband to the NIH, where he was beginning a fellowship in medical genetics at the clinical center. At the time this program was only open to physicians, but over many beers, Dr. Bale persuaded the director of the program to allow her to join. She spent the next 16 years at NIH, where she first completed a postdoc and then served as section head

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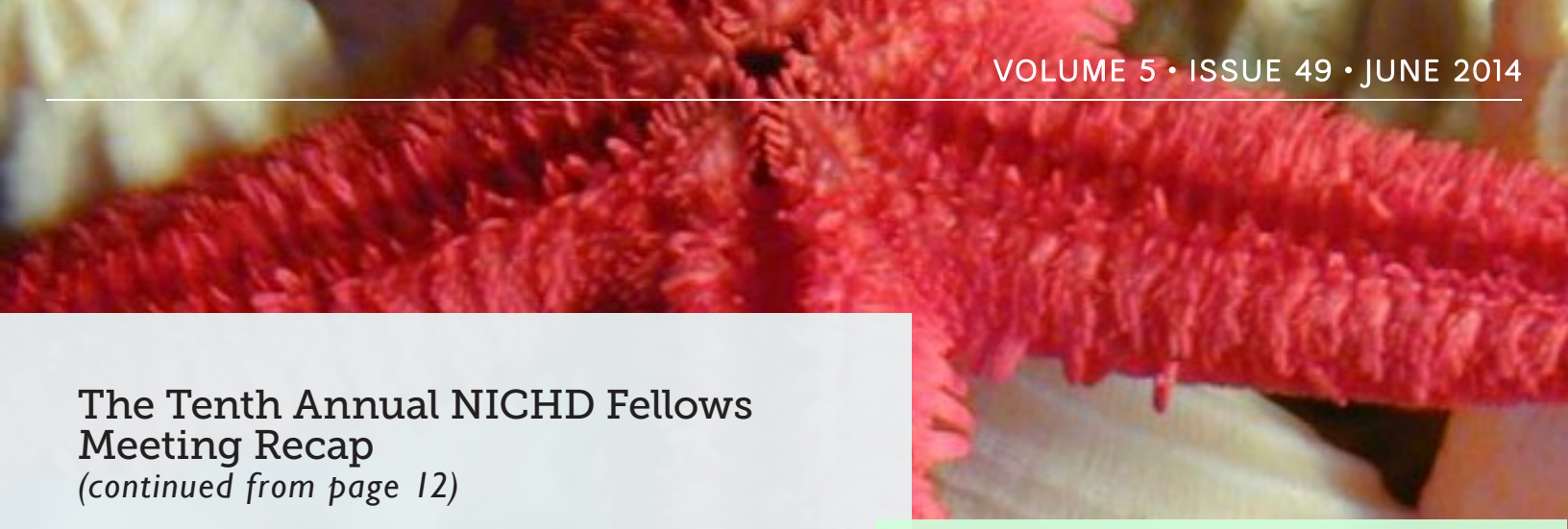

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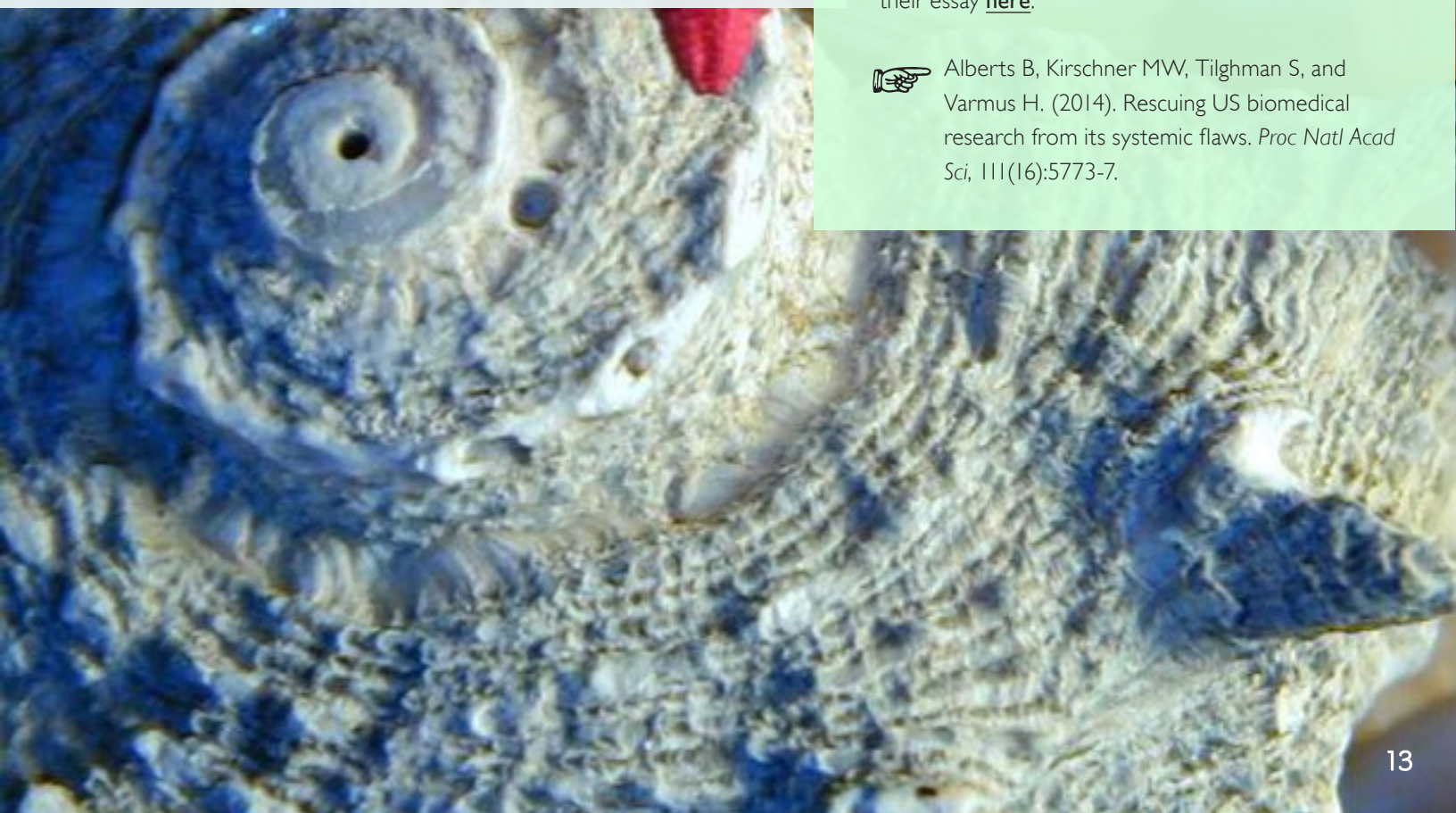
investigating the genetic basis of rare hereditary diseases of the skin.

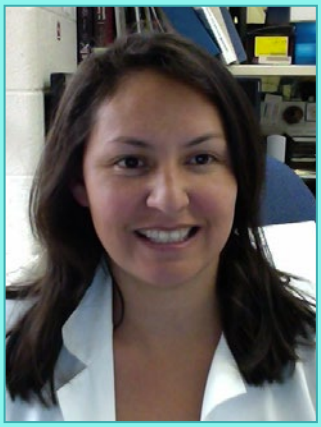
It was in this capacity that she interacted with many families afflicted with hereditable diseases that desperately wanted to know the genetic status of their children. Commercial genetic diagnostic labs didn't exist, so in 2000, Dr. Bale left the NIH and co-founded GeneDx with her former staff scientist. In 2006, BioReference laboratories acquired GeneDx, and Dr. Bale's initial personal investment of $14,000 resulted in a multi-million-dollar profit just six years later. Currently, she serves as Managing Director of GeneDx and Sr. Vice President of BioReference Labs. Dr. Bale's best advice for current fellows is to "do what you love, and the rest will fall into place."

During the ninth annual NICHD fellows meeting, Dr. Shirley Tilghman, president of Princeton University, delivered a keynote address focused on problems with, and possible solutions for, the current state of postdoctoral training and career progression in biomedical sciences (**recapped June 2013**). Now, Dr. Tilghman and several other prominent biomedical researchers have published their thoughts on early career scientists in the Proceedings of the National Academy of Sciences. Their essay, "Rescuing US biomedical research from its systemic flaws," examines "the source of the dilemma," dangers of hypercompetition, and how the current research climate is affecting the next generation of scientists. To read their recommendations for change, check out their essay **here**.

Alberts B, Kirschner MW, Tilghman S, and Varmus H. (2014). Rescuing US biomedical research from its systemic flaws. *Proc Natl Acad Sci*, 111(16):5773-7.



June Announcements



Dr. Tamara James

CONGRATS TO DR. TAMARA JAMES, NEW AAAS FELLOW

Dr. Tamara James, our first Fellows Recruitment Incentive Award recipient, recently accepted a new position as an AAAS fellow starting September 2014. She will be working within the NIDCR Office of the Director on several initiatives, including the NIH Secretary's Tribal Advisory Committee meetings. Dr. James completed her postdoc in Dr. Mike Cashel's lab. Please join *The NICHD Connection* in congratulating Dr. James on this exciting opportunity!

CONGRATS TO DRS. NELLA AND NILSSON ON GRADUATING

Congratulations to our two graduating Pediatric Endocrinology sub specialty fellows, Dr. Katerina Nella and Dr. Ola Nilsson, who are leaving for positions at the University of Texas Medical Branch in Galveston, TX, and Karolinska Institute, respectively.

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June Announcements

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FULBRIGHT SCHOLAR OPPORTUNITIES

The Fulbright Scholar competition for academic year 2015-2016 launched in February, and many countries are offering awards that target scholars in various fields that relate to cancer. The Council for International Exchange of Scholars administers the Fulbright Scholar Program in partnership with the U.S. Department of State Bureau of Educational and Cultural Affairs. The following is a sample of the awards:

Belgium #5168: Postdoctoral-Junior Research Award in Cancer Clinical and Translational Research

This award is open to postdoctoral researchers who would spend 12 months at the European Organization for Research and Treatment of Cancer (EORTC) in Brussels. The selected candidate will receive training in the methodology of cancer clinical and translational research using data from EORTC databases. This award prefers applicants who specialize in cancer research, pathology, and translational research; health technology; epidemiology; bioinformatics; statistics; and molecular biology, in particular genomics.

France #5218: Alsace Regional Award

This research award is open to all levels of scholars, including early career, who are interested in doing research in a variety of fields including medical imaging, medical devices, physical and life sciences, and chemistry. The scholars would affiliate with an institution in the Alsace region in France. A potential host institution for this award is the Institut de Recherche Contre Les Cancers de L'appareil Digestif in Strasbourg.

Ireland #5263: Medical Sciences/Nursing

This teaching/research award is open to experienced academics with a strong record of publication who will predominantly focus on research in a variety of nursing research areas such as cancer trajectory and chronic illness management, among others. The scholar would be affiliated with the Catherine McAuley School of Nursing and Midwifery at the University College Cork.

Jordan #5429: Nursing

This teaching, teaching/research, or research award is open to clinical nurses. The selected candidate will teach undergraduate and graduate courses at one of the three eligible host institutions. Oncology and maternity and women's health are among the preferred specializations.

More information about the Fulbright Scholar Program can be found at http://www.cies.org, and the complete catalog of awards can be accessed online at http://catalog.cies.org. As outlined in the Eligibility Guidelines, all applicants must be U.S. citizens at the time of application. **The current competition will close on August 1, 2014.**

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June Announcements

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BUILDING AN EFFECTIVE TEAM: INTERVIEW AND HIRING PRACTICES IN THE SCIENCES

For tenure-track investigators, assistant clinical investigators, research fellows, and 5th/final year postdocs:

The NICHD is offering a two-hour workshop on Monday, June 16th, from 11-1, led by a PhD scientist, Diane Epperson, and a workforce planning expert, Elaine Brenner.

Interviewing for lab members may seem straight forward – hire smart skilled people. However, building dynamic, cohesive teams that adapt to the ever changing directions of science requires a variety of hiring strategies. This training session is designed to introduce helpful processes and tools to enhance your ability to attract, interview, hire and retain the top talent for your lab.

Learning Objectives:

- Gain insight into using a scientific hiring process to identify and select best fit candidates, including guidelines and success factors for each step
- Learn successful interview formats, strategies, and tips, including behavioral interviewing techniques
- Increase skills in using consistent, objective measures to evaluate candidates and support selection decisions

Space is limited. Please contact Brenda Hanning (HanningB@mail.nih.gov) if you would like to attend.

For research fellows and postdocs, please note that the workshop is for those of you who will be transitioning to academe or the private sector in the coming year.

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June Announcements

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CALL FOR POSTER ABSTRACTS

This is a call for poster abstracts for the 2014 NIH Research Festival, to be held from September 22 to 26. The Research Festival is the annual showcase of NIH intramural research. Drs. Catherine Bushnell and Michael Krause, the Festival co-chairs, encourage submissions from all research areas, but request a limit of one poster submission per first author.

To submit a poster abstract:

1. Visit http://researchfestival.nih.gov/forms/poster.cgi
2. Enter poster information.
3. Submit form by **11:59 p.m., June 16, 2014**.

June Events

MONDAY, JUNE 16, 11 – 1 PM

Building an Effective Team: Interview and Hiring Practices in the Sciences
With Dr. Diane Epperson & Elaine Brenner
See Announcements on **pg 16** for additional information





TENTH ANNUAL

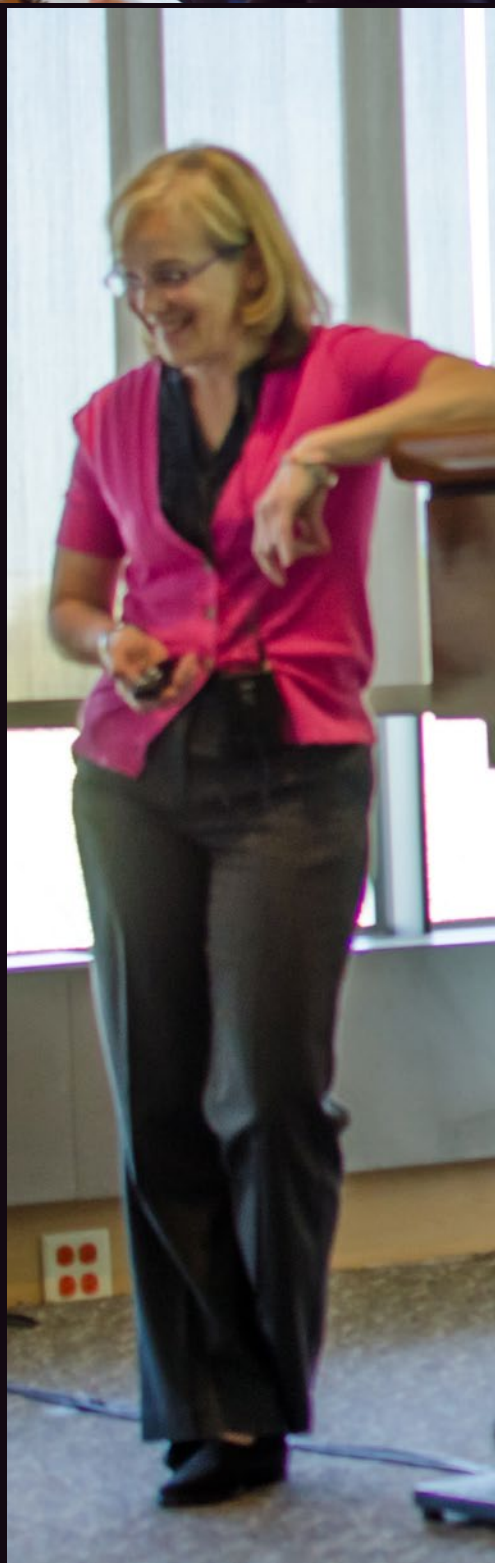
NICHD

Fellows Meeting

APRIL 21, 2014







10TH
ANNUAL MEETING
OF POSTDOCTORAL, CLINICAL, & VISITING FELLOWS
& GRADUATE STUDENTS
MONDAY, APRIL 21, 2014
SMITHSONIAN NATIONAL MUSEUM OF THE AMERICAN INDIAN
WASHINGTON, DC
REGISTRATION & ABSTRACT DEADLINE:
FRIDAY, MARCH 14, 20


COLORADO
ELEVATION
14,259
LONGS PEAK
ESTES PARK


Growth Curve Comparison
Primer Extensions
Infection with dksA complementation
Background